



NATIONAL HEALTH
LABORATORY SERVICE

GeneXpert MTB/RIF

Progress Report

October 2014





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1. Background to Project

This project was initiated at the request of the Honorable Minister of Health, Dr Aaron Motsoaledi, in early 2011, following the World Health Organization's strong recommendation published in December 2010 which stated that "the new automated DNA test for TB be used as the initial diagnostic test in individuals suspected of MDR-TB or HIV/TB". In essence this comprises the majority of TB suspects in South Africa. A pilot study was proposed by the TB Cluster within the National Department of Health (NDoH) while a project feasibility study was being performed with due diligence.

The pilot study was initiated in microscopy centres. The NDoH requested that at least 1 instrument be placed in each province, preferably in high burden districts. Selections were made by the TB cluster, with twenty-five microscopy centres being selected and a total of 30 instruments placed.

The NDoH funded 9 GX16 and 14 GX4 instruments for the project. FIND (The Foundation for Innovative New Diagnostics) donated 6 GX4 analysers and the Infinity or GX48 was supported by PEPFAR Right to Care funds. All instruments were placed by World TB day March 24 2011. This placement represented about 10% of national coverage. The basis for the calculations was an assumption that 2 smears at diagnosis would be replaced by 1 Xpert® MTB/RIF assay. All instruments were interfaced to the NHLS Laboratory Information System (LIS) allowing for troubleshooting and data collection.

Since then, 296 GeneXpert instruments of varying sizes (GX4: 98; GX16:190; GX48: 1; GX80:7) have been placed in 216 sites – both urban and rural settings, by the National Priority Programmes of the NHLS and the NDoH, the progress of which is described in point 6 below.

The programme is being further expanded to directly support the annual screening for TB and HIV of a quarter of a million people in special risk populations in correctional centres and in peri-mining communities. There are 6 districts with high proportion of mines in South Africa that have been identified for focused attention.



1.1. Correctional Services

In order to improve TB control in all 242 correctional facilities in South Africa, the NHLS is working in partnership with the Department of Correctional Services (DCS), NDoH, Aurum Institute, TB/HIV Care Association and Right to Care to ensure access to regular HIV- and TB-related screening, testing and treatment of up to 150,000 offenders through the Global Fund programme. Xpert MTB/Rif testing is being provided either on-site, or at the nearest referral laboratory. During 2014, Xpert MTB/RIF testing facilities have been established on-site at the following Correctional Facilities:

- Kgoši Mampuru Management Area II
- Barberton Management Area
- Johannesburg Management Area
- Groenpunt Management Area
- Pollsmoor Management Area
- St Albans Management Area
- Durban-Westville Management Area

1.2. Peri-Mining Communities

NHLS, together with the Aurum Institute, has been appointed by NDoH (under the Global Fund grant) to provide services to implement interventions aimed at improving TB and HIV/AIDS management for vulnerable peri-mining communities (estimated at around 600,000 people) in 6 main mining districts. Six staffed and GeneXpert-equipped mobile TB units will be provided within the communities to undertake Xpert MTB/RIF testing for TB. In addition, persons newly identified as HIV-infected through the clinical partner will be staged for HIV-treatment using CD4 tests provided by the closest NHLS lab in the district. The 6 districts with a high proportion of mines in South Africa that have been identified for focused attention are:

- Lejweleputswa (Free State),
- Dr K K Kaunda & Bojanala Districts (North West),
- West Rand (Gauteng)
- Waterberg & Sekhukhune (Limpopo)

2. Assays performed to date

In summary, a total of 4,411,399 specimens have been processed to date (30 September 2014). In September 221,944 specimens were processed. The total % of *Mycobacterium tuberculosis* complex (MTBC) detected in this cohort was 9.76% (21,661). As a reflection of Xpert MTB/RIF's superior sensitivity over microscopy, the average national TB positivity rate among suspects was found to be 8% using microscopy but up to 16-18% in the first year and 13-14% in the second and third year, and has remained constantly around 12% in the fourth year, after introduction of Xpert® MTB/RIF assay. To date Kwa-Zulu Natal (KZN) has performed the greatest number of tests which is probably as a result of the number of instruments placed (refer to tables 1 & 2). Average Rifampicin resistance detection rates have remained around 7% since project inception (Refer to tables 3 & 4).

Table 1: GeneXpert MTB Results by province (cumulative)

Province	Year	MTB Detected	MTB Not Detected	Test Unsuccessful	Total	% MTB Detected
EASTERN CAPE	2011	3 252	15 235	549	19 036	17,08
EASTERN CAPE	2012	15 880	84 755	2 862	103 497	15,34
EASTERN CAPE	2013	45 469	320 022	10 046	375 537	12,11
FREE STATE	2011	2 811	14 532	35	17 378	16,18
FREE STATE	2012	11 660	76 863	288	88 811	13,13
FREE STATE	2013	14 758	139 299	1 020	155 077	9,52
GAUTENG	2011	3 094	18 881	443	22 418	13,80
GAUTENG	2012	11 120	72 979	2 305	86 404	12,87
GAUTENG	2013	31 432	215 064	7 690	254 186	12,37
KWAZULU-NATAL	2011	7 546	30 575	896	39 017	19,34
KWAZULU-NATAL	2012	23 963	135 973	5 915	165 851	14,45
KWAZULU-NATAL	2013	42 294	293 200	15 003	350 497	12,07
LIMPOPO	2011	1 973	17 253	173	19 399	10,17
LIMPOPO	2012	4 004	30 924	689	35 617	11,24
LIMPOPO	2013	13 927	188 932	6 086	208 945	6,67
MPUMALANGA	2011	2 629	12 683	1 100	16 412	16,02
MPUMALANGA	2012	4 035	22 226	1 133	27 394	14,73
MPUMALANGA	2013	10 406	63 030	2 210	75 646	13,76
NORTH WEST	2011	3 429	14 557	644	18 630	18,41
NORTH WEST	2012	5 499	29 977	2 052	37 528	14,65
NORTH WEST	2013	13 301	100 512	4 926	118 739	11,20
NORTHERN CAPE	2011	2 727	15 527	712	18 966	14,38



NORTHERN CAPE	2012	3 830	21 728	1 038	26 596	14,40
NORTHERN CAPE	2013	7 912	53 728	2 529	64 169	12,33
WESTERN CAPE	2011	2 173	9 897	47	12 117	17,93
WESTERN CAPE	2012	13 206	68 045	689	81 940	16,12
WESTERN CAPE	2013	28 653	155 003	2 343	185 999	15,40
EASTERN CAPE	2014	40 514	320 075	9 433	370 022	10,95
FREE STATE	2014	11 792	108 487	810	121 089	9,74
GAUTENG	2014	32 773	260 871	6 418	300 062	10,92
KWAZULU-NATAL	2014	48 615	441 241	15 826	505 682	9,61
LIMPOPO	2014	12 203	185 055	6 644	203 902	5,98
MPUMALANGA	2014	12 351	95 711	3 549	111 611	11,07
NORTH WEST	2014	14 477	130 413	5 735	150 625	9,61
NORTHERN CAPE	2014	7 370	53 812	2 528	63 710	11,57
WESTERN CAPE	2014	27 727	149 527	1 663	178 917	15,50
TOTAL		538 805	3 966 592	126 029	4 631 426	11,63

Table 2: GeneXpert MTB Results by province (01-31 October 2014)

Province	MTB Detected	MTB Not Detected	Test Unsuccessful	Grand Total	% MTB Detected
Eastern Cape	3 578	29 117	1 091	33 786	10,59
Free State	1 361	11 620	72	13 053	10,43
Gauteng	3 838	29 770	795	34 403	11,16
Kwa-Zulu Natal	5 322	51 154	2 213	58 689	9,07
Limpopo	1 362	19 150	789	21 301	6,39
Mpumalanga	1 225	9 584	505	11 314	10,83
North West	1 514	13 086	612	15 212	9,95
Northern Cape	819	6 203	280	7 302	11,22
Western Cape	2 893	16 652	258	19 803	14,61
Grand Total	21 912	186 336	6 615	214 863	10,20



Table 3: Provincial GeneXpert RIF Results in MTB detected cases (01-31 October 2014)

Province	Inconclusive	Resistant	Sensitive	No Rif Results	Grand Total	% Rif Resistance
Eastern Cape	85	244	3 245	4	3 578	6,82
Free State	28	101	1 231	1	1 361	7,42
Gauteng	79	245	3 509	5	3 838	6,38
Kwa-Zulu Natal	101	465	4 751	5	5 322	8,74
Limpopo	48	68	1 244	2	1 362	4,99
Mpumalanga	16	100	1 109		1 225	8,16
North West	49	92	1 372	1	1 514	6,08
Northern Cape	8	53	756	2	819	6,47
Western Cape	75	132	2 686		2 893	4,56
Grand Total	489	1 500	19 903	20	21 912	6,85

Table 4: Provincial GeneXpert RIF Results in MTB detected cases (cumulative)

Province	Year	Inconclusive	Resistant	Sensitive	No RIF Result	Total	% RIF Resistant
EASTERN CAPE	2011	33	248	2919	52	3 252	7,63
EASTERN CAPE	2012	213	1077	14456	134	15 880	6,78
FREE STATE	2011	28	155	2626	2	2 811	5,51
FREE STATE	2012	162	755	10717	26	11 660	6,48
GAUTENG	2011	25	179	2889	1	3 094	5,79
GAUTENG	2012	136	766	10142	76	11 120	6,89
KWAZULU-NATAL	2011	64	592	6875	15	7 546	7,85
KWAZULU-NATAL	2012	417	2166	21128	252	23 963	9,04
LIMPOPO	2011	25	148	1775	25	1 973	7,50
LIMPOPO	2012	52	268	3609	75	4 004	6,69
MPUMALANGA	2011	30	207	2386	6	2 629	7,87
MPUMALANGA	2012	57	401	3501	76	4 035	9,94
NORTH WEST	2011	39	303	3083	4	3 429	8,84
NORTH WEST	2012	75	414	5000	10	5 499	7,53
NORTHERN CAPE	2011	28	186	2511	2	2 727	6,82
NORTHERN CAPE	2012	50	236	3536	8	3 830	6,16
WESTERN CAPE	2011	15	107	2050	1	2 173	4,92
WESTERN CAPE	2012	153	653	12397	3	13 206	4,94
EASTERN CAPE	2014	1091	2470	36909	44	40 514	6,10
FREE STATE	2014	337	705	10746	4	11 792	5,98
GAUTENG	2014	700	1964	30086	23	32 773	5,99
KWAZULU-NATAL	2014	1319	4185	42916	195	48 615	8,61
LIMPOPO	2014	292	602	11264	45	12 203	4,93



MPUMALANGA	2014	342	1088	10902	19	12 351	8,81
NORTH WEST	2014	435	792	13241	9	14 477	5,47
NORTHERN CAPE	2014	188	367	6805	10	7 370	4,98
WESTERN CAPE	2014	559	1449	25718	1	27 727	5,23
EASTERN CAPE	2013	1274	2969	41073	153	45 469	6,53
FREE STATE	2013	372	800	13564	22	14 758	5,42
GAUTENG	2013	921	2008	28433	70	31 432	6,39
KWAZULU-NATAL	2013	1076	3704	37079	435	42 294	8,76
LIMPOPO	2013	299	715	12803	110	13 927	5,13
MPUMALANGA	2013	238	1024	9116	28	10 406	9,84
NORTH WEST	2013	325	730	12219	27	13 301	5,49
NORTHERN CAPE	2013	175	422	7025	290	7 912	5,33
WESTERN CAPE	2013	636	1409	26606	2	28 653	4,92
Total		12 181	36 264	488 105	2 255	538 805	6,73

3. Rif Concordance

Rifampicin concordance is good for both LPA and culture. The data is skewed by reporting the GeneXpert immediately, but still have to wait for MGIT and LPA results.

Table 5: Rif Concordance by LPA or DST

		GeneXpert Confirmation & Rif Concordance									
Province	Rif Resistant Cases	Cultures					LPA				
		Confirmed		Rif Concordance		Pre-analytical	Confirmed		Rif Concordance		Indeterminate
		#	%	#	%		#	%	#	%	
Eastern Cape	5 514	213	3,9%	138	64,8%	3	1 393	25%	1 290	92,6%	5
Free State	1 903	166	8,7%	95	57,2%	0	643	34%	523	81,3%	146
Gauteng	4 116	160	3,9%	109	68,1%	4	1 067	26%	968	90,7%	20
Kwazulu-Natal	9 673	2 221	23,0%	2 069	93,2%	0	2 117	22%	1 857	87,7%	80
Limpopo	1 451	85	5,9%	69	81,2%	2	335	23%	260	77,6%	9
Mpumalanga	2 369	532	22,5%	523	98,3%	0	870	37%	749	86,1%	2
North West	2 506	143	5,7%	103	72,0%	0	799	32%	681	85,2%	31
Northern Cape	962	202	21,0%	152	75,2%	3	367	38%	281	76,6%	22
Western Cape	3 281	96	2,9%	26	0,0%	0	2 583	79%	2 403	93,0%	2
National	31 775	3 818	12,0%	3 284	86,0%	12	10 174	32%	9 012	88,6%	317



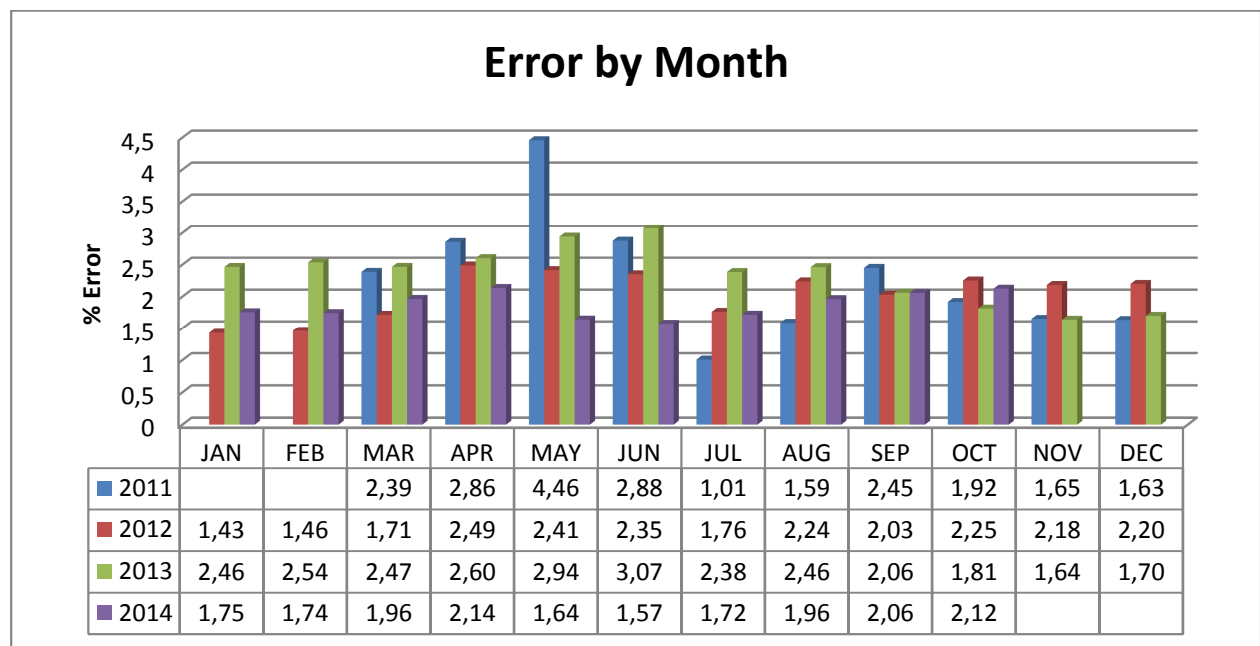
4. Errors

Average error rate has ranged consistently below 3% and Mpumalanga provinces reported error rates above 3%. Details of the invalid results, which likely represent sample issues remains below 1%. These are being monitored regularly and corrective action implemented where necessary.

Table 6: Number of Unsuccessful Tests and Reasons (1-31 October 2014)

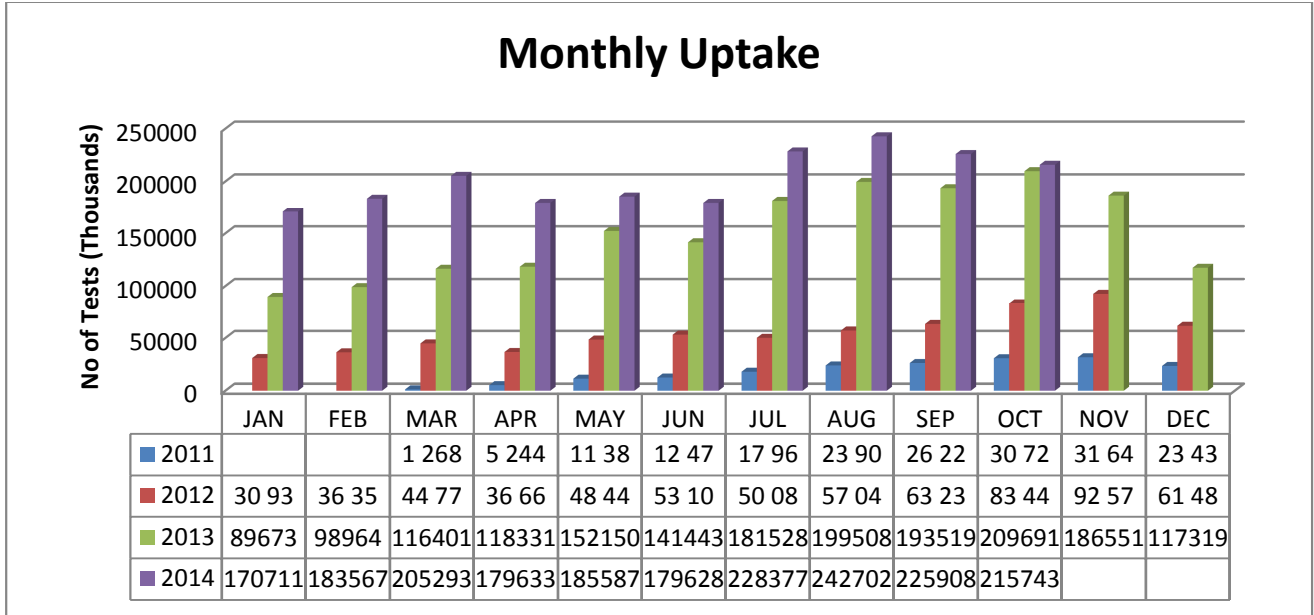
Province	Error	Invalids	No Results	MTB Results	Grand Total	% Error
Eastern Cape	768	283	40	32 724	33 815	2,27
Free State	65	5	2	13 048	13 120	0,50
Gauteng	642	119	34	33 716	34 511	1,86
Kwa-Zulu Natal	1 412	670	131	56 681	58 894	2,40
Limpopo	492	264	33	20 533	21 322	2,31
Mpumalanga	410	85	10	10 816	11 321	3,62
North West	450	112	50	14 627	15 239	2,95
Northern Cape	183	94	3	7 022	7 302	2,51
Western Cape	142	68	48	19 961	20 219	0,70
Grand Total	4 564	1 700	351	209 128	215 743	2,12

Figure 1: GeneXpert Error by Month



5. Monthly uptake since implementation started

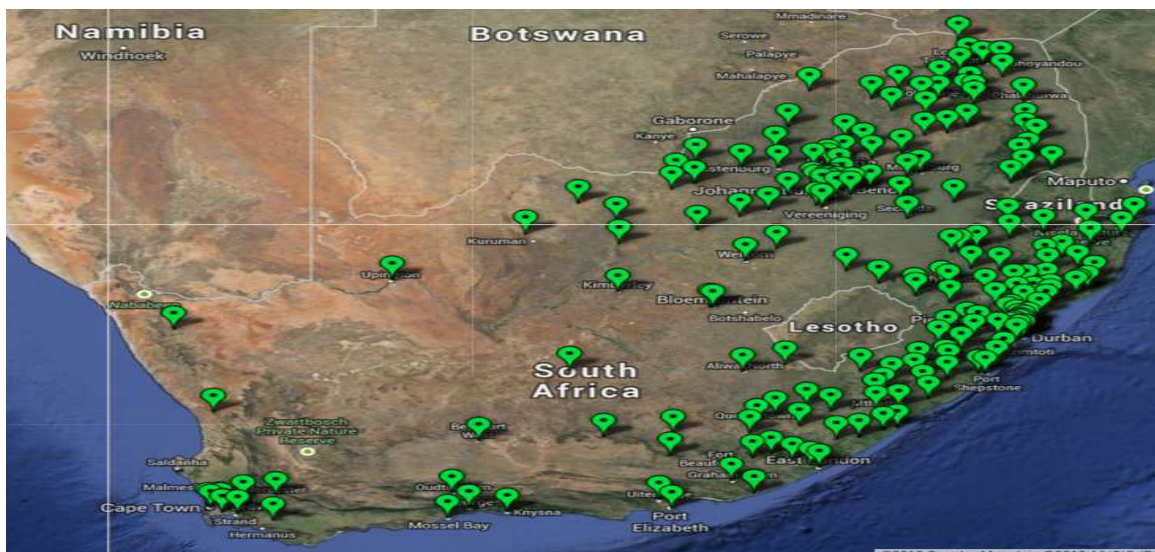
Figure 2: GeneXpert Monthly Uptake



Monthly uptake increased steadily since program inception. The main reason for interruptions is due to the variation in work practices which is expected during the December period.

6. Phased Implementation Progress

Figure 3: Current GeneXpert Placement (207 testing centers, 295 analysers, Gx4: 98; Gx16-8: 1; Gx16: 188; GX48:1; GX80-80: 7) *20 clinic placements *7 Correctional Facilities



7. Training: Laboratory and Clinical

A total of 1,650 laboratory staff and 7,656 health care workers have been trained since December 2011. This will be an ongoing process to support NDoH training on clinical algorithm. Laboratory staff received both clinical and technical training.

8. Challenges identified during the course of the project to date

- Rollout of EGK to avoid duplications
- Implementing WHO recommended guidelines for Xpert testing on EPTB and paediatric samples: being addressed
- EPTB training to be expanded to correctional facilities to ensure compliance
- Hospital staff not complying to the GXP testing algorithm because trainings has not been conducted in most of the hospitals- being addressed
- Staff rotation in hospital wards posing a challenge in the implementation and compliance to the TB algorithms resulting to delay in initiating patients on TB Treatment

9. Literature Update For GeneXpert

There has been an expansion of the literature with respect to the assay performance. The highlights are summarized in the table below:

Table: Recent publications (GeneXpert for pulmonary TB and extrapulmonary TB)

Manuscript	Aim/Sample population and specimen type (n=...)	Results	
		Sensitivity	Specificity
Mathys et al, Int J Tuberc Lung Dis. 2014	A case study describing a discrepant case of smear-positive pulmonary tuberculosis that was Xpert-resistant but phenotypically susceptible to RMP	<ul style="list-style-type: none"> • They repeated Xpert, Genotype® MTBDRplus assay and sequencing of the rpoB gene • Revealed the presence of a silent mutation in the rpoB gene, leading to the conclusion of a false-positive Xpert result. • Caution against misinterpretation of Xpert results which may lead to inappropriate treatment • The presence of rpoB mutations should be confirmed by sequencing the rpoB gene 	
Langley et al, Lancet Glob Health. 2014	Used an integrated model to assess the effects of different algorithms of Xpert MTB/RIF and light-emitting diode (LED) fluorescence microscopy in Tanzania	Identified three strategies as cost effective in Tanzania. <ul style="list-style-type: none"> • Full scale-up of Xpert = greatest population-level effect with the highest incremental cost • The incremental cost-effectiveness ratio 	



		<p>(ICER) of Xpert scale-up was below the willingness-to-pay threshold for Tanzania</p> <ul style="list-style-type: none"> • Same-day LED fluorescence microscopy was the next most effective strategy followed by LED fluorescence microscopy 	
Reither et al, J Infect. 2014	<p>A prospective, multi-centre study evaluated the performance of Xpert MTB/RIF to diagnose pulmonary tuberculosis in children in Tanzania and Uganda</p> <p>n=451</p>	<p>Xpert MTB/RIF assay had a sensitivity of 68% (95% CI, 50%-82%).</p> <p>Xpert detected 1.7 times more culture-confirmed cases than smear microscopy.</p>	<p>Xpert had a specificity of 100% (95% CI, 97%-100%).</p>
Pang et al, Pediatr Infect Dis J. 2014	<p>Evaluated the Xpert for diagnosis of smear-negative childhood pulmonary TB using gastric lavage aspirates (GLA) in Beijing</p>	<p>The sensitivity in detecting children with a clinical diagnosis of TB for MGIT was 12.1% (95% CI: 9.3-14.9%) and for Xpert was 48.6% (95% CI: 44.4-52.8%)</p>	
Ou et al, Int J Infect Dis. 2014	<p>Evaluated the performance of Xpert MTB/RIF in the county-level tuberculosis (TB) laboratory in China</p> <p>N= 2142 suspected non-MDR-TB cases and 312 suspected MDR-TB cases</p>	<p>For MTB detection in suspected non-MDR-TB cases, the sensitivity of MTB/RIF was 94.4%.</p> <p>The sensitivity in smear-negative patients was 88.8%.</p> <p>For the detection of rifampin resistance in suspected MDR-TB cases, the sensitivity of MTB/RIF was 87.1%</p>	<p>For MTB detection in suspected non-MDR-TB cases, the specificity of MTB/RIF was 90.2%.</p> <p>For the detection of rifampin resistance in suspected MDR-TB cases, the specificity of MTB/RIF was 91.0%</p>
Yağmur et al, Mikrobiyol Bul. 2014	<p>Comparison of two different real-time PCR systems (Qiagen and Xpert) in the postmortem diagnosis of Mycobacterium tuberculosis infections in paraffin-embedded tissues.</p> <p>N=40</p>	<ul style="list-style-type: none"> • 72.5% (29/40) concordance between Qiagen and Xpert • 17.5% of samples were positive with Xpert system but negative with the Qiagen • 10% samples were positive with Qiagen but negative with the Xpert system • Xpert MTB/RIF was more favourable to detect M.tuberculosis DNA in paraffin-embedded tissues, with the advantages of determination of rifampicin resistance 	



10. Update on GeneXpert Research projects:

11.1. GeneXpert Verification and EQA program using Dried Culture spots (DCS)

- Panel 3 of the 2014 EQA program is being prepared for November
- New countries joining the EQA program: Swaziland and Namibia
- TBGxMonitor™ (www.tbgxmonitor.com) upgrade specification finalized.
 - Seriuin continue to publish updated components which are undergoing verification and validation.
 - Development validation to begin from 1 September.

11.2. Connectivity solutions for the GeneXpert

- Connectivity: Collaboration with Cepheid ongoing
 - i. Remote connectivity – old dashboard still up to collect routine data ~ 2.1mil results to date
 - ii. Awaiting feedback on the data generated from the beta trial.

11.3 mHealth solutions for MDR-TB

An mHealth project together with the John Hopkins University (JHU) group and funded through the Global Fund has commenced. The first 3 sites in Port Shepstone (Murchison Hospital, Gateway Clinic and Gamalakhe) will receive their first training in the second week of February 2015, with the target launch of the mHealth system is end of February 2015. It was agreed that the data sharing will be conducted through the CDW Initial review of the web-service interface being discussed. Additional options for possible mHealth applications for pilot are currently being investigated.

11. Update on other projects

- **Evaluation of the GeneXpert to Diagnose Paediatric TB using stool specimens:** (In collaboration with David Alland and FIND). The laboratory R&D component to determine appropriate stool processing protocol has started. Phase 1a completed and involved 30 spiked TB positive and 30 TB negative specimens tested using 6 different stool processing and filtration protocols. Phase II starting November.



- **Longitudinal follow up of Dried Blood Spots for viral load monitoring:** Longitudinal collection of DBS from n=100 HIV-positive patients on ARV's over 60 weeks. Outstanding final visit (V5) DBS for testing.
- **Development of DCS EQA for LPA:** EQA test panels consisting of DCS have been provided to 4 routine labs (x3 panels each) as a pilot evaluation of the format on the MTBDR*plus* LPA (Hain LifeScience). A short form paper has been drafted for publication.
- **Laboratory validation of new TB diagnostics:** 1). A validation protocol is underway for evaluation of the updated Abbott NM high throughput TB assay. The clinical study has begun: n=59 patients have been recruited to date and tested on the new Abbott assay for comparison to MGIT culture and smear.
- **Laboratory validation of new HIV diagnostics:** Two new HIV VL evaluations of POC diagnostics are planned: 1). A pilot evaluation of the new Alere q VL POC instrument (Alere Inc) on whole blood which provides a VL result in 52 min - Protocol in preparation for November start 2). A laboratory evaluation of the Cepheid HIV-1 Quantitative VL cartridge on plasma, DBS and whole blood. Awaiting kits and training.
- **GCC Connectivity**
 - No specific update. The connectivity solutions are not being used at present since the study is not recruiting any further patients or performing new tests.

12. Funding

Table 9: Total and Percentage Contribution to date by Donor

Donor	% Contribution
NDoH	24.04
Bill & Melinda Gates Foundation	7.20
TB Reach	1.42
MSF	0.90
FIND	0.45
USAID	2.45
CDC NHLS 2010/11	14.78
CDC NDoH	0.72
CDC NHLS 2011/12	1.39
Dr. Niebauer	0.20
Gobal Fund NDOH	40.91
Global Fund RTC	2.78



CDC NDoH	2.77
Subtotal	100

CDC has contributed 19, 65% towards the program to date.

13. Recent Campaigns

None in the month of October